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Pathobiology of Inflammation to Cell Death

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When a cell dies in vivo, the innate immune system investigates the scene of the crime. If the death of the cell is physiological (eg, occurring as part of normal cell turnover), then the corpse is cleared, and little else is done. In fact, as part of this process, phagocytes that ingest normal apoptotic cells can actively suppress tissue responses by elaborating anti-inflammatory cytokines [1]. But if the cell has died unexpectedly from some pathological process, then the innate immune system expands its investigation.

The earliest response to abnormal cell death is an acute inflammatory response. In this process, dead cells stimulate the production of proinflammatory mediators by the monocytes/macrophages that result in increased blood flow, leakage of protein-rich fluid from venules, and recruitment of neutrophils, followed by monocytes to the site of damage [2]. The recruited leukocytes attempt to clear the corpses and stimulate tissue repair. This process resolves once the stimulus (ie, cell death and/or associated factors) driving these events is removed and the damage is repaired. Recently, interleukin (IL)-1 was shown to be a key mediator in the recruitment of neutrophils [3]. Other innate mechanisms that sense abnormal cell death and the mediators that orchestrate the inflammatory response in this setting remain poorly understood, however.

In parallel to the inflammatory process, the innate immune system also may mobilize the adaptive immune system to respond to antigens associated with dying cells. As part of this process, dendritic cells internalize antigens from dead cells and present them as peptides bound to major histocompatibility class (MHC) class I and MHC class II molecules [4]. In addition, dead cells can stimulate dendritic cells to migrate to secondary lymphoid tissue and mature into an immunostimulatory state [5]. Through these mechanisms, dendritic cells alert T cells to potential pathological situations in the peripheral tissues that are causing cells to die. If CD4 or CD8 T cells recognize antigenic peptides presented on the MHC molecules of the mature and stimulatory dendritic cells, then an adaptive immune response is initiated.

Why are the innate and adaptive immune systems so concerned with cell death? The current notion is that if cells are dying under nonphysiological conditions, then there is an underlying pathological process, and this is potentially dangerous to the host. According to this idea, the innate immune system has evolved mechanisms to detect this potential danger [6,7]. When death is detected, the ensuing acute inflammatory response rapidly delivers the soluble and cellular defenses that attempt to neutralize or "wall off" the injurious process and ultimately repair the damage. Similarly, cell death alerts the adaptive immune system to a potential problem in ways that will mobilize this arm of the immune system if immunogenic antigens are present.

These immune responses are double-edged swords. On the one hand, they rapidly mobilize host defense to the potential problem before it gets out of control, but on the other hand, the acute inflammatory response is indiscriminant and can damage normal tissue [7]. Although this may be a small price to pay for containing an injurious process, there are many settings in which the recruited response is of no benefit (eg, in a sterile ischemic infarct there is nothing to defend against) and actually may make the situation worse. In fact, the cell death–induced inflammatory response is thought to contribute to the pathogenesis of various diseases. Similarly, in individuals so predisposed, dead cells may help stimulate an adaptive response to autologous antigens and contribute to the development of autoimmunity. Given these "costs" and "benefits," the innate immune response to dying cells is medically important.

Precisely how the innate system recognizes cell death and discriminates between normal physiological and pathological cell death is not fully understood. Apoptotic cells express "eat me" signals, like phosphatidyl serine on the outer leaflet of the plasma membrane, that cause phagocytes to ingest these cells and produce anti-inflammatory mediators, such as transforming growth factor β and interleukin (IL)-10 [1]. In contrast, necrotic cells typically provoke inflammatory responses (and adaptive ones if antigens are

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present). Therefore, one factor that influences the host response is the mechanism of cell death. In some situations, however, apoptotic cells also stimulate inflammation and promote the generation of T cell responses.

In some cases (eg, infections where cytopathic microbes are causing cell death), responses to dying cells are stimulated in part by the underlying pathological process. In such a situation, pattern recognition receptors, such as Toll-like receptors (TLR) on leukocytes, can recognize microbial molecules and stimulate inflammation and adaptive immune responses [8]; however, cell death (eg, in sterile situations) itself is sufficient to trigger these responses [7]. This is thought to be because the innate immune system has evolved mechanisms to detect the exposure or release of intracellular molecules that normally are hidden from view in living cells [9]. Thus, the release of these intracellular molecules is a sign of cell damage and potential danger. These immunostimulatory molecules are collectively referred to as danger signals, or damage-associated molecular patterns (DAMPs).

The number of different kinds of DAMPs in cells is unknown. Thus far, several putative DAMPs have been identified. These molecules include uric acid, high-mobility group box 1 (HMGB1) protein, nonmuscle myosin heavy chains, heat shock proteins, and some other molecules. Moreover, more DAMPs almost certainly remain to be discovered [9]. Some DAMPs may stimulate leukocytes directly, whereas others may work by generating mediators from extracellular components by cleaving extracellular matrix proteins or activating complement. There also is relatively limited information regarding which receptors sense the release of DAMPs and stimulate the immune responses. There is evidence that TLR-2 and -4 sense cell death and in particular HMGB1, but these molecules appear to play a relatively minor role in triggering the inflammatory response to dying cells [3]. There also is evidence that the intracellular pattern recognition receptor NLRP3 (NALP3, cyropyrin), is involved in the generation of IL-1β and inflammatory responses to the DAMP uric acid [10], but its role in the response to dying cells remains unknown.

Ultimately, to gain more insight into the inflammatory response to cell death, it will be necessary to identify the various DAMPs that trigger this process and elucidate the pathways that they stimulate. This is crucial to understanding the biology of these responses and how they contribute to health and disease. Moreover, because cell death–induced immune responses contribute to disease pathogenesis, these pathways are potential molecular targets for therapeutics to modulate the cell death–induced immune responses.

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